Progressive mental deterioration in old age has been recognized and described throughout history. However, it was not until the early part of the 20th century that a collection of brain cell abnormalities were specifically identified by Dr. Alois Alzheimer, a German physician, in 1906. He diagnosed a woman who had died after years of experiencing severe memory problems, confusion, and difficulty understanding questions. In 1901, a 51-year-old woman, Auguste D, was admitted to the state asylum in Frankfurt. She was suffering from cognitive and language deficits, auditory hallucinations, delusions, paranoia and aggressive behaviour, and this was studied by Dr. Alois Alzheimer (1864–1915). Today, this degenerative brain disorder bears his name. Dr. Alzheimer moved to the Munich medical school in 1903 to work and discuss about his patient with Dr. Emil Kraepelin – one of the foremost German psychiatrists of that era who later, coined the term, “Alzheimer’s Disease”.

Famous people who suffer from the degenerative neurological Alzheimer's disease (AD) remind us that there is currently no prevention, no cure, and no discrimination when it comes to diagnosis. Political figures, actors, and athletes can use their recognition to bring attention to the need for research, early diagnosis, and increased awareness. Perhaps the most well-known sufferer, of course, was the 40th President of the United States, Ronald Reagan. Besides him, the modern American conservative of the 60s, Barry Goldwater, who also died of Alzheimer's in 1998, lived his last years in private. Sir Winston Churchill, the Prime Minister of Great Britain, suffered from Alzheimer's Disease or a dementia associated with strokes though some experts are not really sure. And last but not the least Muhammad Ali, a renowned boxer was also a victim of this disease.
Risk Factors:

For many diseases, it is possible to show a single cause. For example, a virus is known to be the cause of measles. However, for chronic disorders (long-lasting conditions), there is still much about the causes that is unknown. It is thought that multiple causes working together are more likely to cause certain conditions.

In their search for answers, scientists look for factors which are more common in people who develop a particular disease. The presence of these 'risk factors' is associated with an increased chance that the disease will develop.

Risk factors are characteristics of a person (e.g. blood group) or environmental (e.g. sunlight) which appear to have some relationship to the development of a disease. Other examples include exposures to a substance or product, family background or work history. Thus, a person who smokes is more likely to develop lung cancer than someone who does not smoke. The well established risk factors of AD are as follows:

- **Age:** The risk of developing Alzheimer's disease appears to double every 5 years survived beyond age 65, when about one in 100 people have Alzheimer's. This increases to 25 in 100 over the age of 85.

- **Family history of early onset Alzheimer's disease: familial Alzheimer's disease (FAD):** People who have two generations or more of first degree relatives (parent or sibling) with early onset (age 65 or under) Alzheimer's disease have a greater chance of developing the disease than those with no family history.

It is important to remember that this rare form of the disease, Familial Alzheimer's Disease FAD) only accounts for 1 per cent of all cases and is known to be entirely inherited. FAD is passed directly from one generation to another through a
dominant inheritance pattern. This means that if a parent has FAD each child has a 50 per cent chance of inheriting FAD.

- **Genetic risk factors in late onset Alzheimer's disease:** In late onset (over the age of 65) Alzheimer's disease certain genes appear to influence a person's susceptibility to developing the disease. The most important gene discovered to date is the Apolipoprotein E gene, which is found on chromosome 19. This gene occurs in three forms in humans: types 2, 3, and 4. Every person in the world carries two Apolipoprotein genes: they can be the same type (2,2; 3,3; or 4,4) or a mixture of two types (2,3; 2,4; 3,4). It has been found that people with at least one type 4 (especially those with two, i.e., 4,4) are at increased risk of developing Alzheimer's disease earlier in life than those with the other types of Apolipoprotein E. People with type 2 (especially 2,2) appear to be protected against developing Alzheimer's disease, until much later in life.

- **Down syndrome:** Most people with Down syndrome who live long enough to late adulthood, develop Alzheimer's disease pathology.

- **Lifestyle.** The same factors that put you at risk of heart disease, such as high blood pressure and high cholesterol, may also increase the likelihood that you'll develop Alzheimer's disease. Poorly controlled diabetes is another risk factor. And keeping your body fit isn't your only concern — you've got to exercise your mind as well. Some studies have suggested that remaining mentally active throughout your life, especially in your later years, reduces the risk of Alzheimer's disease.

- **Education levels.** Studies have found an association between less education and the risk of Alzheimer's. Some researchers theorize that the more we use our
brain, the more synapses we create, which provides a greater reserve as our age. It remains unclear, however, whether less education and less mental activity create a risk of Alzheimer's or if it's simply harder to detect Alzheimer's in people who exercise their minds frequently or who have more education.

- **Toxicity.** One long-standing theory is that overexposure to certain trace metals or chemicals may cause Alzheimer's. For a time, aluminum seemed a likely candidate, because some people with Alzheimer's have deposits of aluminum in their brains. After many years of studies, however, no one has been able to link aluminum exposure directly to Alzheimer's. At this point, there's no evidence that any particular substance increases a person's risk of Alzheimer's.

- **Head injury:** Individuals who have sustained a head injury (defined as causing loss of consciousness for at least 15 minutes) have a small but statistically significant greater chance of developing Alzheimer's disease than those who have not had a head injury.

- **Female sex (a slight risk factor):** Women have a slightly greater chance of developing Alzheimer's disease than men, even when allowance is made for their longer life span. Scientists are investigating whether hormone replacement therapy reduces this risk.

**Neuropathological Hallmarks of Alzheimer's Disease:**

Alzheimer's disease (AD) is the most common chronic neurodegenerative disorder and the leading cause of dementia especially in the Western countries. The onset of disease is rarely before the age of 60 and after that period the incidence and prevalence rise with increasing age (Amaducci, 1997). AD is clinically manifested by progressive memory loss and a general decline in
cognitive function. With progression of disease due to severe cortical dysfunction, patient becomes demented, aphasic, disorientated, immobile and emaciated. Pneumonia or urinary infections are the common causes of death.

**Morphological Changes**

There is cortical atrophy with narrowing of gyri, widening of sulci and hydrocephalus ex vacuo. Most severely affected are temporal lobes (hippocampus, parahippocampus, and amygdala), than frontal and parietal lobes. Occipital lobes and motor cortex are usually spared. The disease is characterized by deposition of beta amyloid protein in cerebral cortex and dramatic loss of neurones and synapses. A number of important neuropathological changes occur in the brains of AD.

**Neurofibrillary tangles (NFTs)**

NFTs are considered to be a major pathological hallmark of Alzheimer’s disease. Alois Alzheimer (1907) was the first who described the NFT in the soma of cortical neurons in a 51-years old women who had a 5-year history of progressive dementia. NFTs develop within the pyramidal neuronal soma as argentophilic filamentous inclusions, which extend into the neuronal processes. They are flame or globoid in shape. After deterioration of the parent cell, the NFT persists in the neuropile for a long time as an extraneuronal structure. NFT consists of highly insoluble and proteolysis-resistant paired helical filaments (PHF) in addition to 15 nm wide straight filaments and amorphous material of unknown biochemical composition. PHFs are composed of protofilaments containing proteins that are immunologically related to normal cytoskeletal proteins. PHFs appear as left
handed double helices with diameter of 20-24 nm and periodicity of 160 nm. The main subunits of PHFs are altered forms of microtubule associated tau protein which undergo abnormal phosphorylation (Trojanowski et al., 1993). Abnormally phosphorylated tau protein is believed to be neurotoxic and can be the cause of neuronal death. Apart from perikaryal NFT, PHFs are also found in dystrophic neurites associated with plaques formation and neuropil threads (Braak et al., 1986). Besides tau protein, the immunoreactivity for beta amyloid protein (beta /A4 protein) and ubiquitin can be found in NFT (Perry et al., 1982). In general, NFTs show a rather striking predilection to affect particular areas of the AD brains. Their density is highest in the pyramidal neurones of the medial temporal lobe (amygdala, CA1 area of hippocampus, subiculum, layers II and IV of the entorhinal cortex) and moderate in the layers III and V of the association cortex of the frontal, temporal and parietal lobe. The major subcortical neurones affected by NFT are cholinergic neurones of the basal nucleus of Meynert, noradrenergic neurones of locus coeruleus and serotonergic neurones of raphe nuclei. The characteristic and laminar distribution of NFTs supports the hypothesis that pathological process in AD may spread along a sequence of corticocortical connections between the association cortical areas and the hippocampal formation. The NFTs occur in neuron clusters that give rise to the feed forward and feedback cortico-cortical projections occurring between cortical and subcortical region (Armstrong, 1993). The loss of these systems leads to the disconnection between hippocampus and neocortex and between neocortical association areas resulting in the disintegration of intellectual function (Terry, 1994).
Neuritic plaques (NP)

Neuritic (amyloid, senile) plaques are foci of enlarged axons, synaptic terminals and dendrites, associated with extracellular beta/A4 amyloid. They appear as spherical areas with amyloid-positive core surrounded by argentophilic material. NPs are generally confined to the cerebral cortex. The sites of predilection are amygdala, CA1 area of hippocampus, subiculum and layers II, III and V of the entorhinal cortex. There are several plaque subtypes. The two most prominent are diffuse and classic plaques. Diffuse or immature plaque consists of beta/A4 in a non-aggregated form, free of any neuritic involvement. This form should be aggregated at some stage of the disease. It was shown that beta/A4 deposits promote neuritic interactions that result in neurite dystrophy. Classic plaque consists of fibrils of aggregated beta/A4 core surrounded by clear halo with dystrophic neurites (DN), activated microglia and reactive astrocytes at the periphery. DN within plaque consists of distended axons, dendrites and synaptic terminals. DN exhibits immunoreactivity for amyloid precursor protein, growth associated protein (GAP43), tau, ubiquitin and neurofilaments (Braak et al., 1986; Mc Kee et al., 1991).

Neuropil threads (NTs)

NTs appear as argentophilic network of fragmented and twisted fibers in the neuropil. They are formed within axons, dendrites and presynaptic terminals. NTs are often associated with NFTs, but are independent of NPs. Ultrastructurally, NTs are composed of PHF. Immunohistochemical techniques revealed that they contain tau and ubiquitin (Braak et al., 1986).
Hirano’s bodies (HBs)

HBs are eosinophilic intraneural structures, most often found in the hippocampal pyramidal neurones. They are best seen in H&E preparations. Ultrastructurally HB consists of crystalloid arrays of interlacing filaments displaying either a lattice-like or herringbone configuration (Hirano et al., 1968).

Granulovacuolar bodies (GVB)

GVBs appear as round vacuoles (3-4 microns) with a dense core which stains blue in H&E and are argentophilic. They are confined to the soma of hippocampal pyramidal neuron. (Hirano et al., 1968). The significance of HB and GVB is unknown.

Cerebral amyloid (congophilic) angiopathy (CAA)

CAA appears as an accumulation of beta/A4 amyloid filaments within walls of small arteries and arterioles of the leptomeninges and cerebral cortex. Beta/A4 can also be deposited within cerebral cortical capillaries when it usually makes a spikelike projections into the brain parenchyma (Okazaki et al., 1979). CAA is rarely demonstrable in the white matter and brainstem. CAA may be the cause of small cortical infarcts and hemorrhage.

Abnormalities in neurotransmitter level

Loss of basal forebrain cholinergic neurons

The best documented changes in activities of transmitter enzymes in AD patients are found in the cholinergic system. Acetylcholine (ACh), the transmitter released
by cholinergic neurons, is synthesized by choline acetyltransferase (ChAT) and catabolized by acetylcholinesterase (AChE), the major component of cholinesterase (AChE). Many different subtypes of muscarinic receptors, of Ach for example, M1 and M2, have been found. The M2 receptor subtype is a presynaptic and M1 receptor subtype is a postsynaptic receptor of Ach. The first reported changes in reductions of the ChAT and AChE activities have been observed in the neocortex, hippocampus and many other brain regions in autopsy samples of AD (Whitehouse, 1997). A significant deficit of ChAT in AD has been found in the frontal, parietal cortical and temporal cortical regions, hippocampus and amygdala, the decrease being the most severe in younger AD patients (Braak et al., 1994; Geula and Mesulam, 1994; DeKosky and Scheff, 1996; Lander and Lee, 1998).

The reduction in ChAT activity and the number of senile plaques in the cortex are correlated with the loss of neurons in the nucleus of Meynert (Bronfman et al., 2000). Demonstration by immunohistochemical methods of both ChAT and AChE in the senile plaques further has emphasized the involvement of cholinergic neurons in AD (Abe et al., 1994). In addition, the staining of AChE in the cortex has been observed to be profoundly reduced in patients with AD (Bronfman et al., 2000). Extensive evidence has implicated the medial septum in learning and memory. Lesions of the medial septum impair acquisition and retention performance in a variety of behavioral paradigms (Abe et al., 1994). Furthermore, memory can be enhanced or impaired by intra-septal infusions of drugs that act at a variety of neurotransmitter systems (Jaffar et al., 2001). The septum contains cholinergic cell bodies that project to the hippocampus via the fimbria fornix (Geula C and Mesulam, 1994). Furthermore, lesions of the medial septum or the
fimbria fornix eliminate hippocampal theta rhythm, an effect that is associated with memory deficits (Geula C and Mesulam, 1994). Extensive evidence indicates that the septo-hippocampal system is involved in memory processes (Dwaine and Thomas, 1990). More specifically, the role of the medial septum in learning and memory appears to involve an influence on cholinergic processes in the hippocampus (Abe et al., 1994). Lesions of the septo-hippocampal pathway decrease extracellular acetylcholine (ACh) levels in the hippocampus (Geula C and Mesulam, 1994). Like the effects of septal lesions, the memory-modulating effects of intra-septal drug infusions also appear to involve cholinergic processes in the hippocampus. Intra-septal infusions of the cholinergic antagonist scopolamine, at doses that impair learning and memory, also decrease extracellular cholinergic levels in the hippocampus (Gorman et al., 1994). Intra-septal infusions of muscimol (Ach inhibitor) prevent training induced increases in hippocampal ACh (Moor et al., 1998) and reduce high-affinity choline uptake (HACU), ACh turnover rate, and extracellular ACh levels in the hippocampus (Moor et al., 1998). Glucose is linked to the synthesis of ACh. Furthermore, glucose elevates extracellular ACh levels in the hippocampus of behaving rats (Ragozzino et al., 1998) and increases hippocampal HACU when the hippocampal cholinergic system is pharmacologically challenged (Micheau et al., 1995). These results suggest that the medial septum may influence memory via a process that also involves an effect on the ACh system in the entorhinal cortex.
In hippocampus, Pyramidal cells of the CA1 region express high levels of 5-HT1A-receptor mRNA and 5-HT1A-receptor binding (Pompeiano et al., 1992). Early on, intracellular recordings in brain slices showed that the 5-HT-induced inhibition was caused by hyperpolarization resulting from an opening of K⁺ channels (Segal, 1980). Subsequent work, in which various pharmacologic approaches have been used in brain slices, has shown that the 5-HT induced inhibition in both CA1 and CA3 pyramidal cells is mediated by the activation of receptors of the 5-HT1A subtype (Andrade and Nicoll, 1987). After long-term but not short-term administration of various antidepressant treatments (selective 5-HT reuptake inhibitors, monoamine oxidase inhibitors, tricyclic drugs, electroconvulsive therapy), disinhibitory responses are seen with the selective 5-HT1A antagonist WAY 100635, which suggests increased 5-HT1A-mediated inhibitory tone on CA3 hippocampal pyramidal cells (Haddjeri et al., 1998). In addition to the above-mentioned direct effects on pyramidal cells, 5-HT has been shown to depress both excitatory and inhibitory synaptic potentials in the hippocampus. Relatively high concentrations of 5-HT cause a reduction in electrically evoked excitatory postsynaptic potentials (EPSPs) in CA1 pyramidal cells (Schmitz et al., 1995⁵), an effect that is mimicked by 8-OH-DPAT, which suggests mediation by 5-HT1A receptors. Indirect measures indicate that 5-HT acts presynaptically to reduce Ca²⁺ entry and thereby glutamatergic synaptic transmission. In addition, a 5-HT1A-mediated inhibitory effect on putative inhibitory interneurons of the hippocampus has been observed (Schmitz et al., 1995⁶). Clearly, the effects of 5-HT in the hippocampus are highly complex,
involving both presynaptic and postsynaptic actions that may, to varying degrees, be inhibitory or disinhibitory, facilitative or disfacilitative.

In cerebral cortex, neurons typically display mixed inhibitory and excitatory responses to 5-HT because of expression by the same pyramidal cells of multiple 5-HT receptor subtypes (e.g., 5-HT1A and 5-HT2/2C) (Araneda, 1991). Hyperpolarizing responses mediated by 5-HT1A receptors are often unmasked or enhanced in the presence of 5-HT2 antagonists, consistent with the idea that an interaction occurs between 5-HT1A and 5-HT2A receptors at an individual neuronal level (Lakoski and Aghajanian, 1985). In addition to the above-mentioned postsynaptic effects, various presynaptic effects are mediated by 5-HT1 receptors in the cerebral cortex. In cingulate cortex, 5-HT, acts on presynaptic 5-HT1B receptors, reduces the amplitude of electrically evoked EPSPs (Tanaka and North, 1992).

Involvement of Norepinephrine in memory processing

Evidence exists that the adrenergic system has an important role in normal CNS function as well as in brain disease. The LC, the predominant source of noradrenergic projection neurons in the brain, is significantly damaged in AD (Ishino and Otsuki, 1975). Although adrenergic receptors in these projection areas of AD brains have been studied, and some abnormalities have been observed (Kalaria et al., 1989; Meana et al., 1992), there have shown variable results. Limbic regions of the brain, such as the frontal neocortex and hypothalamus, are projection regions of the LC known to contain significant levels of NE and adrenergic receptors, and function in the modulation of behavior (Weiger and Bear, 1988). The cerebellar cortex is another LC projection area
that has been shown to participate in behavioral control, in addition to motor control (Schmahmann, 1991). Recent studies have indicated new evidence for involvement of the NE–LC system in memory. Inactivation of the PGi (a major input to the LC, described above) with either lidocaine or the GABA agonist muscimol immediately after acquisition in a one-trial inhibitory avoidance task produced marked deficits on a retention test given 48 hours later. (Clayton and Williams, 2000). These findings suggest that pharmacologic manipulation of PGi neuronal activity may affect memory formation via influences on LC and subsequent NE release in brain systems involved in the encoding of new information. Recent studies by Przybyslawski et al., 1993 have also indicated a role for the LC–NE system in memory. These experiments indicate that memories are normally reconsolidated each time they are reactivated by relevant cues. They found that blockade of adrenoceptors after memory reactivation, during the consolidation process, produced impairment on future tests of the same memory. This NE dependent lability of active memory traces indicates a novel mechanism to target in pharmacologic manipulation of memory-related disorders, such as posttraumatic stress disorder and Alzheimer’s disease.

**Involvement of Dopamine in memory processing**

DA also appears to have a role in short- and long-term synaptic plasticity within the striatum. Specifically, DA was found to influence two opposite types of synaptic plasticity within the striatum that depend on the history of synaptic input. In cases in which striatal excitatory amino acid afferents arising from the cortex are stimulated with high frequencies in the absence of magnesium (to enhance NMDA conductances), a long-term facilitation in synaptic transmission is induced, known as long-term potentiation. In contrast, if the stimulation is carried
out at a low frequency, the opposite type of plasticity is induced; that is, long-term depression (LTD) (Calabresi et al., 2000). These forms of synaptic plasticity have been proposed to play a major role in learning and memory formation in other structures, such as the hippocampus. Such plasticity within the striatum may be involved in such phenomena as the acquisition of complex motor skills. Repetitive stimulation of corticostriatal fibers to release glutamate is required for the induction of LTP and LTD, which only occurs in the presence of DA afferent input (Centonze et al., 1998). Thus, D1 and/or D2 antagonist pretreatment prevents the induction of LTD (Calabresi et al., 2000), suggesting that a synergistic interaction between these receptor subtypes is required for this process to occur. In contrast, cortical stimulation-induced LTP is blocked selectively by D1 antagonists, but is actually enhanced by D2 antagonists or in D2 receptor knockout mice (Calabresi et al., 1997).

**Hypobaric hypoxia and memory loss**

High altitude (HA) exposure is characterized by hypobaric hypoxic environmental conditions that induce changes in both physiological and psychological responses. The defense personnel, mountaineers, rescue persons etc are mostly exposed to such environment. In HA they are subsequently prone to several diseases including acute mountain sickness, high altitude pulmonary edema, high altitude cerebral edema etc. and in many of them dysfunction of brain occurs which leads to memory loss (Asplund et al., 1998). Experimental oxygen deprivation or hypoxia leads to various alteration of the central nervous system (CNS) which is evident from behavioral disorders and also several other anatomical, cytological and many various biochemical alterations. It has been considered that HA exposure is an extreme physiological stress that may induce a
variety of harmful effects at neuronal level in brain. Hypoxia can be correlated with central cholinergic hypo function in the hippocampus and caudate nucleus, which is manifested by almost concomitant changes in cholinergic markers in these areas (Speiser et al., 1990). Circumstantial evidence for the relevance of the cholinergic lesion to the clinical features of dementia comes from many pharmacological studies showed that cholinomimetics induce symptomatic improvement in both mild and advanced dementia, in senile as well as presenile forms of Alzheimer's disease (Martin et al., 2000; Baskin et al., 1999).

There is currently scanty report for the hypothesis that amyloid plaques (AP) or neurofibrillary tangles (NFT) are caused by the loss of cholinergic innervations. But it has been found that there is a complex interaction between cholinergic neurotransmission and amyloidogenesis as well as tau phosphorylation (Sadot et al., 1996).

It is now well established that chronic exposure to high altitude lead to disturbance in CNS. Bhatia et al., 1969 demonstrated that hypobaric hypoxia at the altitude of around 5400 meters could distort normal sleep mechanism. Work from this laboratory has reported that hypoxic exposure at this altitude leads to altered behavioral pattern in memory task together with the alteration of brain monoamines, which also have a potent role in memory (Ganguly and Guha, 2006).

Treatment of Alzheimer's disease

Treatment of Alzheimer's is a complex and multifactor process, involving both pharmaceutical and non-pharmaceutical approaches.
Although there have been many recent advances in the understanding of the pathological process of Alzheimer's disease, there still remain limited therapeutic approaches. There are only three approved drugs, and the remainder are still in the experimental stage - some yet even to be tested in humans.

Pharmacological Treatment

1. **Cholinesterase inhibitors**

Currently there are only three drugs approved by The Food and Drug Administration (FDA), all of which are acetyl cholinesterase inhibitors.

   a) **TACRINE (Cognex)**
   
   b) **ARICEPT (Donepezil hydrochloride)**
   
   c) **EXELON (Rivastigmine)**

Acetylcholinesterase usually acts to break down the neurotransmitter acetylcholine. Therefore if it is inhibited by acetylcholine esterase inhibitors, acetylcholine is given extra time to transmit messages.

Neuronal losses resulting from this degenerative disease largely affects the cholinergic system, which has a key role in cognitive functioning and is essential for memory formation. Acetylcholine is commonly used by neurons in the hippocampus and cerebral cortex, regions usually affected by Alzheimer's. Therefore by increasing the levels of acetylcholine, these drugs compensate the cholinergic deficit.

Tacrine only appears to help some patients for a period of time ranging from months to a few years. Trials have shown only modest improvement in tests of
memory and cognition in about 40% of sufferers. They also did not show any improvement in other functional measures which affect quality of life. Side effects include nausea and abdominal cramps, aggression, irritability, skin rashes, headaches and hepatotoxicity in some patients.

**Aricept**, most commonly used drug to combat mild to moderate symptoms. It only appears to help some patients for a period of time ranging from months to a few years.

**Exelon**: Clinical trials show that it improves the patient’s ability to carry out normal day to day activities.

Interestingly, it has been suggested that it is a protein called **prostate apoptosis response-4 (Par-4)** that reduces acetylcholine, by firstly reducing its production and secondly by triggering apoptosis. Research is currently underway into blocking the production of Par-4 to increase the levels of acetylcholine.

Side effects due to anticholinergic properties include dry mouth, blurred vision, constipation, urinary retention, impotence, postural hypotension (in the elderly), hypothermia (in the elderly), hypersensitivity reactions, cholestatic jaundice, blood dyscrasias, photosensitive dermatitis and ocular complications.

### 2. Nootropic agents

These are benzoyl piperidine compounds known as ampokines and include Piracetam and Aniracetam. The mechanism by which they are thought to act is unclear, although it has been proposed that it is through potentiation of glutamate.
they up-regulate receptors. Although their efficacy has not been proven in humans, animal models have shown improvement in learning and memory.

3. **Improved blood flow / psycho-stimulation**

This group works through vasodilation or the effects on monoamine receptors, and includes Dihydroergotoxine and Pentoxyfylline. Again their efficacy has not been proven in humans, although there have been many trials.

4. **Nerve growth factors**

Nerve growth factors (NGF) are the best known of a group of compounds known as **neurotrophic factors**, which are aimed at improving growth and nutrition of neural tissue in the body. NGF specifically is required for the survival of the forebrain cholinergic neurons that are affected in Alzheimer's. Shortage of this growth factor favours neuronal apoptosis. (Programmed cell death.)

The **pathology** of Alzheimer's disease leads to the shrinking and loss of the ability to make acetylcholine. A study in the Sake Institute in California found this could be reversed in aged rhesus monkeys. Fibroblasts were genetically modified to secrete NGF and then grafted directly into affected regions of the brain. This proved so successful that researchers have now initiated privately-funded clinical trials to test the efficacy and safety in humans.

5. **Anti-inflammatory drugs**

Inflammation is always present in Alzheimer's, although it affects remains unclear. It is possible that inflammation may be a beneficial process, in so much as it may stop the **accumulation of amyloid**, although strong epidemiological
evidence suggests that anti-inflammatory agents such as steroids and NSAIDs (non steroidal anti-inflammatory drugs) are associated with a decreased risk of Alzheimer's.

A recent study comparing the effects of the steroid prednisone and a placebo showed no noticeable beneficial effects. There have also been studies into the specificity of selective COX-2 inhibitors over joint COX-1 and COX-2 inhibitors.

6. Antioxidants

It is thought that free radicals contribute to Alzheimer's disease by causing chain reactions which cause oxidative damage to cells. Many studies have shown that they can be controlled by free radical scavengers, or antioxidants including vitamin E, vitamin C, ginkgo biloba, flavonoids, carotenoids and their use in delaying/preventing Alzheimer’s is now being investigated. It is also thought that the beneficial effect of oestrogen in Alzheimer’s is due to its antioxidant affect.

Ginkgo Biloba is being tested by the National Centre for Complimentary and Alternative Medicine and the NIA among others to determine whether it can prevent or delay dementia in older individuals. The results were inconclusive however, as 60% of participants failed to complete the study.

7. Inhibitors of excitotoxicity

These include glutamate antagonists, calcium-channel blockers and protease inhibitors. They are mainly being developed in other areas, such as strokes, as there is little evidence to support the role of excitotoxicity in the pathogenesis of Alzheimer’s.
8. **Inhibitors of amyloid formation**

Many experts believe that abnormal processing of the APP is one of the central pathological events in Alzheimer's. Similarly beta-amyloid (Aβ) accumulations are the main components of the amyloid plaques. Thus much investigation is ongoing into APP processing and beta-amyloid aggregation, including the possibility of a vaccine. This will stimulate the immune response against beta-amyloid, as well as blocking the secretase enzymes, which cleave APP into beta-amyloid.

Beta-amyloid aggregation can also be blocked by the chemical chrysamine G and a dye called Congo red. Although they are both effective theoretically, they cannot cross the blood-brain barrier. Thus derivatives to overcome this difficulty are now being studied.

9. **Inhibitors of tau protein deposition**

Tau protein plays such a major role in dementia that its presence in cerebrospinal fluid could be used as a diagnostic marker. The inhibitors have not yet been developed, but include inhibitors of tau-phosphorylation.

10. **The role of nicotine**

Surprisingly, studies show that lifelong smokers have a reduced risk of developing Alzheimer's, and improves cognition in man, and produces neuroprotective effects in vitro. Present treatment includes antidepressants, sedatives, antipsychotic drugs, anxiolytic drugs and hypnotic treatment.
Antidepressant therapy may be indicated if symptoms are marked and persistent, although treatment should be regularly monitored. Tricyclic antidepressants are the drugs of first choice, although monoamine oxidase inhibitors are equally effective for milder illnesses.

Antipsychotic drugs also known as Neuroleptics generally tranquilize and are used to quieten disturbed patients whatever the underlying psychopathology. They also alleviate anxiety in low doses. These effects result from the drug blocking central dopamine receptors.

But these have various side effects e.g. Weight gain due to increased appetite, Side effects due to dopamine blockage like parkinsonism, Akathisia (an irresistible motor restlessness), acute dystonia (muscular spasm), tardive dyskinesia (persistent movements predominantly affecting the tongue and other facial muscles), gynaecomastia, galactorrhoea.

Non pharmaceutical treatment

Although there is limited evidence to support their benefits to behaviour improvement, they undoubtedly enhance the patients' quality of life, and thus their use should always be considered on an individual basis.

1. Reality orientation

This involves all those in regular contact with the patient providing orientating clues as much as possible.

It occurs in both group and individual basis. Individually the carers prompt the patient verbally and also with clocks, calendars, signposts and memory boards. In
groups, for example in hospitals and nursing homes, it involves discussing simple information and current affairs. The difficulties in measuring behavioural changes make assessment of this intervention difficult, although it is associated with improved verbal orientation.

2. Reminiscence therapy

This is aimed at improving the mood of patients by exposure to music, films, photographs and foods that help them remember past experiences. It generally takes place in small groups.

3. Behavioural modification

A behaviour analysis is used to devise a strategy that rewards desirable behaviour and reduces undesired behaviour. It is of particular use in patients who exude difficult behaviour.

The aim is to change the patient’s behaviour by altering the triggers and/or the consequences of the behaviour.

Research is also underway into interventions to help patients in the early stages of dementia deal with depression. In addition to modifying their behaviour, they help the patient alter the negative or mal-adaptive thought patterns considered to underlie their behaviour. It is too early for conclusions to be drawn.

4. Occupational activities

Difficult behaviour is often caused by boredom, reduced participation in day-to-day activities and loss of previous interests. The aim here is to engage the patient in activities in order to provide positive stimulation.
Music therapy has been reported to help relieve agitation, although once again it is difficult to assess its efficacy.

Activity programmes are also used as an intervention, and there has been some evidence of a reduction of behavioural disturbance, although again assessment is difficult.

5. Environmental modifications

This involves both changes to the physical environment and changes to care routines. Again the effectiveness of this treatment is hard to evaluate.

6. Validation therapy

This encourages a reflection and validation of the patient's view of reality through looking at life experiences and unresolved conflicts.

7. Sensory stimulation

This intervention is based on the hypothesis that confusion in the elderly can be associated with sensory deprivation and unchanging sensory input. It involves a variety of methods including touch and bright lights. Studies are small however and conclusions cannot yet be drawn.

Herbal approach for Alzheimer’s treatment

The discipline of Ayurveda has existed in India for millennia. One of the practices of Ayurveda is to treat poor health with medicines obtained from herbs. These medicines are prepared from various parts of plants. The medicines are most commonly dispensed in the form of a powder or as a water-based extract that is
prepared as a decoction, much as tea is brewed. Indian herbal substances with psychotropic properties have been described by many researchers. The use of complementary medicines such as plant extracts in dementia therapy, varies according to the different cultural traditions. In China, Ginkgo biloba in which the ginkgolides have antioxidant, neuroprotective, and cholinergic activities relevant to Alzheimer's disease mechanisms. In European origin, a variety of other plants such as Salvia officinalis (sage) and Melissa officinalis (balm) with memory improving properties, and cholinergic activities have recently been identified in extracts of these plants. Precedents for modern discovery of clinically relevant pharmacological activities in plants with long-established medicinal use include, for example, the interaction of alkaloid opioids in Papaver somniferum (Opium poppy) with endogenous opiate receptors in the brain. In India, Acorus calamus, Bacopa monniera, Nardostachys jatamansi, Centella asiatica, Celastrus paniculatus etc. are recently shown to prove memory boosting properties.

Moringa oleifera (MO), commonly called ‘sajna’, a multipurpose tree found almost all over the Asian and African countries and are consumed as food by the people. This plant has several medicinal properties. In rural areas of India, the leaf of MO is chewed as it is believed to act as a brain booster. But there is no scientific evidence for this.

Although this plant is native to India, Arabia and possibly Africa and the East Indies, it has been widely cultivated and naturalized in tropical Africa, tropical America, Sri Lanka, India, Mexico, Malabar, Malaysia and Philippine Islands. It is a short slender deciduous perennial tree which grows to be about 10 metre tall. The leaves of the tree are pale-green in colour and have a feathery appearance.
Plate 1: (a) *Moringa oleifera* tree, (b) *Moringa oleifera* leaf
Uses

i) Folk medicine:

The flowers, leaves and roots of Moringa are still used in folk remedies for tumors and seeds for abdominal tumors. The root is used in Nicaragua for dropsy. Root juice is applied externally as rubefacient or counter-irritant. The bark from the tree is also applied for a variety of skin diseases. The indigenous practitioners of India still prescribe the root of the young tree in cases ranging from intermittent fever, hysteria, palsy to chronic rheumatism and dyspepsia. In fact, some Indian tribal groups use it to counter epileptic attacks (Bodding, 1983). Leaves are applied as poultice to sores, rubbed on temples for headaches and also said to have purgative properties. The bark, leaves and roots are acrid and pungent and taken to promote digestion. In fact, the bark is regarded as antiscorbutic and exudes a reddish gum with properties of tragacanth; sometimes used for diarrhoea. The roots are bitter and act as a tonic to the body and lungs and are used as expectorant and also mild diuretics (Bodding, 1983).

ii) As Food:

Almost every part of the plant is of value as food. The seed is said to be eaten like peanuts in Malaya. Thickened root is used as a substitute for horseradish in Europe. The foliage is eaten as greens, and also used in salads, vegetable curries and in pickles for seasoning (Chatterjee and Pakrashi, 1983).

Chemistry

Per 100 g the pod is reported to contain 86.9 gm of H₂O, 2.5 gm protein, 8.5 gm total carbohydrates, 4.8 gm fiber, 2.0 gm ash, 30 mg calcium (Ca), 110 mg phosphorus (P), 5.3 mg iron (Fe), 184 IU vit A, 0.2 mg niacin, 1.20 mg ascorbic acid, 310 mg copper (Cu), and 1.8 mg iodine (Chatterjee and Pakrashi, 1983).
Leaves contain 7.5 gm of water, 6.7 gm of protein, 1.7 gm of fat, 14.3 gm total carbohydrate, 0.9 gm of fiber, 2.3 gm ash, 440 mg Ca, 70 mg P, 110 mg Cu, 5.1 mg I, 11300 IU vit A, 120 mg vit B, 0.8 mg nicotinic acid, 220 mg ascorbic acid and 74 mg tocopherol compound, β-sitosterol and a pectinesterase are also reported. Leaf amino acids include 6.0 g arg./16 g N, 2.1 his, 4.3 lys, 1.9 trp, 6.4 pala, 1.4 g met, 3.9 g threonine, 6.5 g leu, 4.4 g ile and 5.4 val (Das, 1965).

Aqueous and alcoholic extracts of root and flower of MO were found to show significant antihepatotoxic activity against paracetamol-induced hepatotoxicity in rats (Ruckmini et al., 1998).

An ethanolic extract of fresh pods of MO yields a novel glycoside niazidin possessing an O-nitrile thiocarbamate groups, along with thiocarbamate, carbamate, and isothiocyanate glycosides. Their structures have been determined. Fatty acid ester, long chain hydrocarbons, carbamic acid, isocyanates, sithiocyanates, phenolic esters, nitriles, nitrile ester, polysulphide sulfinate and benzyl thiocarbamate, along with elemental sulfur (S8), have also been identified through GC-MS (Faizi et al., 1995).

The seeds of malunggay, MO were extracted with distilled ethanol and concentrated under reduced pressure at 40°C. The resulting extract was partitioned between hexane, ethylacetate, butanol and water. The solvent fractions were concentrated under reduced pressure. The crude ethanol extract of dried seeds inhibited the carrageenan-induced inflammation in the hind paw of mice by 85% at a dosage of 3mg/g body weight while the mature green seeds by 77%. The hexane fraction of the crude ethanolic extract also inhibited inflammation by 77% at the same dosage while both butanol and water fractions inhibited inflammation by only 34%. The serotonin results indicate the strong inflammatory activities of
the crude ethanol extract and the hexane fraction. The ethyl acetate fraction caused 267% increase in inflammation and inhibited toxicity. The mice died after oral administration of the fraction. The crude ethanol extract also inhibited the formation of Epstein-barr virus early antigen (EBV-EA) induced by 12-0-tetradecanoylphorbol-13-acetate. At a dosage of 100 μg/ml the extract inhibited EBV-EA formation by 100% suggesting its antitumor promoting activity (Caceres et al., 1992; Murakami et al., 1998).

MO is reputed for its medicinal uses. Survey of chemical literature shows that no phytochemical investigation has been undertaken on its stem gum although the presence of different chemical compounds in its seeds, flowers and leaves, has led to the isolation of a new leucioanthocyanin characterized as leudelphinidin-3-O-beta-D-galactopyranosyl (1-4)-O-beta-D-glucopyranoside (Khare et al., 1997).

All parts of MO were taken for clinical trials. Mother tincture of all parts were prepared and tried in different dilutions on patients in the age group of 16-40 years. On the basis of the results obtained it is concluded that homeopathic use of Moringa cure inflammatory and infectious conditions in the whole body due to the presence of pterygospermin. It can also be used in typhoid fever and partial impotency (Maishi et al., 1994).

The root bark of MO contains two alkaloids (Dasputra et al., 1977) (total alkaloids 0.1%) viz. moringine which is identical with benzylamine and moringinine which is belonging to the sympathomimetic group bases. The latter acts on sympathetic nerve endings, producing a rise in blood pressure, acceleration of heartbeat and constriction of blood vessels. It inhibits the tone and movements of involuntary muscles of the gastrointestinal tract and relaxes bronchioles.
**Research work on Moringa oleifera**

It was observed that MO could cure inflammatory and infectious conditions in the whole body due to the presence of pterygospermine. They also found that it can also be used in typhoid fever and partial impotency (Maishi et al., 1994).

An experiment was done on anti-ulcerogenic evaluation of the methnolic extracts of some indigenous medicinal plants of Pakistan in aspirin-ulcerated rats. It was found that *Moringa pterygosperma* flower buds showed some decrease in ulcer index (Akhtar and Ahmed, 1995).

Investigations on the stem gum have led to the isolation of a new lencoanthocyanin characterized as lencodelphinidin-3-0-beta-D-galactopyranosyl (1-4)-beta-D-gluco-pyranoside (Khare et al., 1997).

The ethanolic and aqueous extracts of MO whole pods and their parts were found to have hypotensive activity (Faizi et al., 1995).

Niaziminin, a thiocarbamate isolated from the leaves of MO was proposed as a strict structural requirement for the inhibition of tumor-promoter induced Epstein-Barr virus (EBV) activation (Murakami et al., 1998).

Work on the mineral composition of non-conventional leafy vegetables, found that MO leaf ethanol extract have some oxytocic activity on uterus strips of guina pig and mice (Barmines et al., 1998).

Mekonnen (1999) examined the effects of ethanolic extract of *Moringa stenopetala* leaves and found that leaf ethanol extracts have some oxytocic activity on uterus strips of guina-pig and mice (Mekonnen et al., 1998).

MO also possess antitumor activity (Guevara et al., 1999). Methanolic extracts of MO root contains hematological and hepatorenal functions and was found to contain some alkaloids (total alkaloid -0.2%). They found that the moderate i.p.
doses of crude extract (CE) in weekly treatment change the serum amino transferase and plasma cholesterol levels significantly. High doses of CE increase WBC count and decreases clotting time significantly (Mazumdar et al., 1999).

Tahiliani and Kar showed the role of MO root extract in the regulation of thyroid hormone status in adult Swiss male and female rats and it was suggested that the lower concentration of this plant extract may be used for the regulation of hyperthyroidism (Tahiliani and Kar, 2000).

It was examined that hypocholesterolemic effect of crude extract of MO leaf in high fat diet fed Wistar rats and concluded that, the leaves of MO have definite hypocholesteromic activity (Ghasi et al., 2000).

Okuda et al have done the isolation and characterization of coagulant that was extracted from MO seed by salt nutrition and revealed that MO contains a neutral coagulant in seeds (Okuda et al., 2001).

Nambiar and Seshadri (2001) found Vit A in drumstick leaves which in turn was found valuable in overcoming the problem of Vit.-A deficiency (Nambiar and Seshadri, 2001).

MO exerts its inhibitory action on CNS by alteration of 5-HT, DA and NE. They also reported that aqueous extract of MO potentiate PB sleeping time and increased α-wave (Ray et al., 2003).

The present study deals with the memory potentiating activity of MO in colchicine model of Alzheimer's disease and also in hypobaric hypoxia induced memory loss in rats.